SYSTEM DYNAMICS MODELING VERSUS UREA KINETIC MODELING

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Abstract- **The Kt/V value demonstrates the dose of hemodialysis (HD). However, because of several existing methods for calculating delivered dialysis dose, Kt/V values can, in fact, be different for the same set of pre-/post-dialysis blood urea concentrations. We prospectively compared the "gold standards" of prescribed (urea kinetic model, UKM), delivered (Daugirdas second-generation) Kt/V and values obtained via the other existing formulae with values obtained using the new system dynamics model for calculating dialysis adequacy and session performance to see whether reliance on the latter approach was likely to lead to errors in over- or underprescribing dialysis regimens. Data were processed on 134 dialysis patients. The statistical analysis reveals that system dynamics model Kt/V values were statistically different ($p < 0.05$) from the calculated Kt/V values from other models, except for those Kt/V values calculated according to the Basile ($P = 0.064$), Ijely ($P = 0.475$) and Daugirdas Second Generation ($P= 0.54$).**

Key words: **urea kinetic modelling, hemodialysis; dialysis adequacy, urea kinetic modeling, system dynamics modeling.**

I. INTRODUCTION

The single-pool urea kinetic model (UKM), utilizing "Kt/V" (the normalized whole body urea clearance), is widely used to help assess the adequacy of hemodialysis (HD). In the classic Gotch-Sargent urea kinetic model, the dialysis parameters are used for prescribing the dose of dialysis therapy (i.e., Kt/V) [1]. Recent studies have shown how efficient the use of urea kinetic modeling (UKM) is in the quantification and monitoring of dialysis [2], and also in predicting patient mortality [3]. On this basis, there is increasing recognition of the need for, and acceptance of, Kt/V as a surrogate for dialysis dose delivered in many renal units [4,5]. System dynamics modeling for calculating dialysis adequacy is considered the newest UKM that is based on not only the feedback concept, which is synonymous with a closed-loop control of variables, but also on the cause and effect concept that focuses on how the thing being studied interacts with the other constituents of the system [6,7]. However, the need for some time to be spent using a computer programme has led to attempts to use various 'short-cuts', including 'bed side' Kt/V models, which can be used by nephrologists as they evaluate patients clinically. The estimation of Kt/V by various models—utilizing pre- and post-dialysis blood urea nitrogen (BUN) concentrations—provides a simple technique for calculating the delivered Kt/V value [8-16]. Unfortunately, as has recently been observed [17], these simplifications rely on various assumptions, which, depending on the extent to which they are valid, can lead to very marked, and highly clinically relevant, differences in calculated Kt/V [18]. However, the accuracy of such techniques has been questioned. One possible reason for the noted inaccuracies may be recirculation, both vascular access and cardiopulmonary-related, resulting in some postdialysis blood sampling techniques encountering a diminution in the blood urea concentration [19]. Another possible reason for the inaccuracies is the frequently observed postdialysis rebound of serum urea [20]. In this scenario, the postdialysis blood urea concentration is artificially low (by 10-22%) immediately after HD due to the continued diffusion of urea from the intracellular to the extracellular space. This artificially low urea concentration immediately after dialysis leads to an overestimate of the efficiency of the dialysis calculated by Kt/V (by 15-40%) if the true, equilibrated blood urea concentration is not used in the calculation, which it is not when using the single-pool urea kinetic model (Kt/V_{sp}). The measurement of the urea concentration at equilibrium for determining the equilibrated Kt/V value (Kt/V_{eq}) requires that a blood sample be drawn approximately 30 minutes after HD, which is an encumbrance for dialysis patients. In order to avoid this encumbrance, some formulae for calculating Kt/V_{eq} from Kt/V_{sp} have been developed, the most popular of which is the Daugirdas correction formula [21]. The purpose of this study was to evaluate the best-known bedside simplified model in an attempt to rank these in order of precision and accuracy.

II. METHODOLOGY

Data were processed on 134 dialysis patients (mean age 48.21±13.38, 69 male, 65 female) on 3-times-per-week dialysis regimens. For each patient, age, gender, height, type of vascular access, location of access, pre-weight, post-weight, pre-blood pressure, post-blood pressure, type of dialysate, weight gain and HD duration were recorded. For the study period of 30 days, the following dialysis parameters were unchanged: dialysis session time 240 min (machine start to machine stop); dialysate flow 500 mmin; blood flow 300 ml/min; same dialysis membrane for each patient (1.2 m^2 Cellulosynthetic (homophone), 1.3 m^2 polysulfone and 1.6 m^2 polysulfone); same dialysis machine (Fresenius 4008 B); and same dialysate sodium/calcium/conductivity profile and dialysate temperature. Special attention was paid to the real

dialysis time, so that time-counters were fitted to all machines for all sessions, to record effective dialysis duration (excluding any unwanted interruptions, e.g. due to dialysis hypotensive episodes). For each dialysis session for each patient the following were recorded: BUN at beginning (C_0), and at the end (C_t) of the session (latter obtained 3 min after slowing the pump speed to 50 ml/min, which value correlated extremely well with that of a sample taken 30 min after the cessation of dialysis, true dialysis time T, the intradialytic weight loss (UF), patients dry weight (Wt); and hematological profile was obtained. For this study the dialysis dose Kt/V was calculated according to the Daugirdas, Lowrie, Keshaviah, Barth, Jindal, Calzavara, Ijely, Basile, and Kerr models, as well as the prescribed Kt/V calculated according to UKM [8-16]. For all treatments, the delivered Kt/V values were also calculated as equilibrated values according to the Daugirdas correction formula. Table 1 summarizes the simplified models used for comparison.

TABLE I. Bedside Models For Simplified Calculation Of Kt/V Values

Model	Formula
Lowrie Model	$Kt/V = \ln(C_0/ C_t)$
Jindal Model	$Kt/V = 0.04 ((C_0 – C_t)/C_0 \times 100) – 1.2$
Keshaviah Model	$Kt/V = 1.162 \ln(C_0 / C_t)$
Barth Model	$Kt/V = 0.031((C_0 – C_t)/ C_0 \times 100) – 0.66$
Calzavara Model	$Kt/V = (C_0 – C_t)/((C_0 + C_t) / 2)$
Daugirdas First Generation Model	$Kt/V = –\ln (C_t / C_0 – 0.008 \times t –UF / Wt)$
Basile Model	$Kt/V = 0.023 ((C_0 – C_t)/ C_0 \times 100) – 0.284$
Ijely Model	$Kt/V = 0.018((C_0 – C_t) / C_0) \times 100$
Daugirdas Second Generation Model	$Kt/V= –\ln (C_t / C_0 – 0.008 \times t) + (4 – 3.5 \times C_t / C_0) \times UF / Wt$
Kerr Model	$Kt/V = 0.042 ((C_0 – C_t)/ C_0 \times 100) – 1.48$

Daugirdas correction formula for calculating an equilibrated Kt/V (Kt/Veq) from a single-pool Kt/V (Kt/Vsp):

$$Kt/Veq = Kt/Vsp - (0.6 \times Kt/Vsp/T) + 0.03$$

C_1 = predialysis blood urea concentration; C_2 = postdialysis blood urea concentration; T = dialysis duration (hours); UF = ultrafiltration volume per dialysis (L); W = postdialysis body mass of the patient (kg).

The dialysis dose Kt/V was calculated also according to the system dynamics approach [22]. Figure 1 shows the modeled dialysis adequacy subsystem that is used to calculate the Kt/V based on the other dialysis variables. This subsystem is a part of the overall system dynamics model (SDM) in [22] that was used as a new approach for quantifying and monitoring dialysis session. The calculated dialysis adequacy is based on the second-generation Daugirdas formula, but it was modified to be used from the systems perspective. The Calculated Dialysis Adequacy stock (Dimensionless) is fed into by adequacy increasing rate (Dimensionless/Minute) and is depleted by adequacy decreasing rate (Dimensionless/Minute). The Calculated Dialysis Adequacy stock is an integral of the adequacy increasing rate less the adequacy decreasing rate.

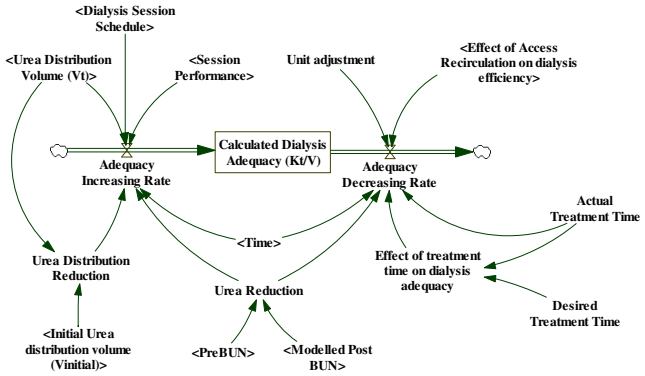

Fig.1 The Dialysis Adequacy Subsystem [22]

Calculated Dialysis Adequacy (t) = Calculated dialysis adequacy (0) + ∫ [adequacy increasing rate - adequacy decreasing rate] dt (1)

Calculated Dialysis Adequacy (0) = 0

The rate of increasing adequacy increases with increase in urea reduction and ultrafiltration rate. An increase in the ultrafiltration rate leads to a decrease in the urea distribution volume and this drives up the dialysis adequacy. Equation (2) represents the adequacy increasing rate:

Adequacy increasing rate = IF THEN ELSE (Session Performance = 1, 0, ZIDZ ((4-3.5 * Urea Reduction) * 0.55 * (Urea Distribution Reduction/"Urea Distribution Volume (Vt)"), Time) (2)

If the session performance is 100 %, this means that the dialysis adequacy reached the desired value. Hence, there is no increase in the adequacy after reaching the value desired. Otherwise, the adequacy increasing rate is driven by the amount of urea removed during session and the reduction in urea distribution volume. The urea reduction is a ratio of the modeled post-BUN to the pre-BUN. The ZIDZ function is used to returns 0 when dividing by 0 to start simulation at initial time. The rate of decreasing adequacy is determined by the amount of urea removed and the small amount of urea generated during dialysis. The recirculation and the adherence to treatment duration also cause a decrease in the dialysis adequacy. Equation 3 represents the adequacy decreasing rate:

Adequacy decreasing rate = (ZIDZ (Ln (Urea Reduction – Unit adjustment * (Actual Treatment Time/60)), Time)) * Effect of Access Recirculation on dialysis efficiency * Effect of treatment time on dialysis adequacy (3)

The product of unit adjustment and prescribed treatment time term adjusts the post-/pre-BUN ratio, R, for urea generation and is a function of session length. For a session length of 3–4 hours, the generation term is about 0.024–0.032. The ratio of the actual treatment time to the desired treatment time determines the effect of the treatment time on dialysis adequacy. The ratio of the reduction of dialyzer clearance by access recirculation (AR) to expected dialyzer clearance determines the effect of the access recirculation on dialysis adequacy. Statistical analysis was performed using SPSS 10.0 and NCSS 2004 software packages using Student's t test, correlation analysis and regressions to the mean. Significance was taken as two-tailed $P<0.05$. For each patient's dialysis session, the absolute difference between the standard and observed Kt/V was derived; by taking all dialysis sessions for all patients, a mean delta (mean of the absolute values of the differences) was derived for each compared method. Also, the mean difference and the standard deviation for that mean difference, along with a 95% confidence interval of those differences, were calculated.

III. Results

The descriptions of the Kt/V results obtained from system dynamics modelling and from the simplified models are shown in Table 2. SDM Kt/V values were statistically different ($p < 0.05$) from the calculated Kt/V values from other models, except for those Kt/V values calculated according to the Basile ($P = 0.064$), Ijely ($P = 0.475$) and Daugirdas Second Generation ($P= 0.54$). For the group as a whole the biggest absolute difference from SDM mean values was obtained using Jindal's, Barth's and Calzavara's models (delta of 0.24, 0.19 and 0.21 respectively ($P<0.05$)). The best correlations were seen with the Daugirdas second generation formula ($R^2= 0.968$).

Table 2. Kt/V results obtained with SDM and simplified models

model	mean	SD	median	min	max
(SDM)	1.201	0.172	1.209	0.61	1.54
Lowrie	1.090	0.151	1.1088	0.611	1.407
Jindal	1.439	0.214	1.481	0.629	1.821
Keshaviah	1.267	0.175	1.288	0.709	1.636
Barth	1.386	0.1655	1.417	0.757	1.681
Calzavara	0.989	0.116	1.008	0.593	1.213
Daugirdas First Generation	1.314	0.199	1.333	0.691	1.803
Basile	1.234	0.1228	1.257	0.767	1.453
Ijely	1.188	9.61E-02	1.206	0.823	1.359
Daugirdas Second Generation	1.213	0.169	1.228	0.647	1.561
Kerr	1.292	0.2242	1.334	0.44	1.692

Also, grouping models containing ln (Co/Ct) terms—Kesheviah, Lowrie, Daugirdas—and those incorporating the (Co–Ct)/Co ratio (i.e. the urea reduction)—Jindal, Barth, Calzavara, Ijely, Basile, and Kerr—there was a better correlation for all models employing the logarithmic transformation (R^2=0.987–0.995 cf. R^2= 0.933–0.94). An overview of the 10 methods comparisons is shown in Table 3.

Table 3. Differences between calculated Kt/V values and Kt/V SDM.

model	Mean*	SEM	95 % LCL of mean	95 % UCL of mean
Lowrie	0.1098	0.019	-0.149	-0.071
Jindal	0.239	0.024	0.193	0.286
Keshaviah	0.066	0.021	0.025	0.108
Barth	0.186	0.021	0.145	0.226
Calzavara	-0.211	0.018	-0.245	-0.175
Daugirdas First Generation	0.114	0.023	0.069	0.159
Basile	0.034	0.018	-0.019	0.069
Ijely	-0.012	0.017	-0.045	0.021
Daugirdas Second Generation	0.013	0.021	00.028	0.054
Kerr	0.092	0.024	0.044	0.139

*Arithmetic mean of the differences between calculated Kt/V and SDM Kt/V; SEM = standard error of the mean; 95% LCL = 95% lower confidence limit of the differences, 95% UCL = 95% upper confidence limit of the differences

IV. Discussion

Numerous studies have confirmed the association between the adequacy of the delivered dose of HD and patient outcome [3]. Held et al. in [3] demonstrated that mortality risk was lower by 7% with each 0.1 higher level of delivered Kt/V. All of this research has confirmed that the Kt/V value represents a very important parameter for chronically hemodialyzed patients. However, calculated Kt/V values have the potential to be used erroneously because of variability in the measurement of the delivered dose. Namely, for the same set of pre-/postdialysis blood urea concentrations, Kt/V values calculated by the various available models could result in a dialysis dose ranging from low and clinically unacceptable to high and clinically adequate [18]. Our results confirmed a statistically significant variability in delivered Kt/V calculation methods, and demonstrated wide differences in resultant Kt/V values. As Kt/V represents an extremely valuable parameter for the dialyzed patient, we recommend that notice be given with regard to the calculation method used in determining every Kt/V value so that the value obtained can be realistically compared to other Kt/V values. That approach would provide an actual adequate dialysis dose per single dialysis treatment. K/DOQI recommends the Daugirdas second-generation formula for delivered dialysis dose (Kt/V) calculation and emphasizes that the literature clearly supports delivery of a minimum HD dose of at least Kt/V = 1.2; however, K/DOQI

does not suggest what constitutes an optimal dose [23]. K/DOQI also recommends that the dose of HD be measured at least monthly. We demonstrated significant differences between Kt/V Daugirdas and other delivered and prescribed Kt/V values. Nonetheless, despite a significant difference, we can advise using Barth's formula as a nonlogarithmic counterpart to the Daugirdas formula. We demonstrated the least mean of the absolute values of the differences to be between SDM's Kt/V values and Kesheviah' Kt/V values. Additionally, we unveiled no significant difference between Daugirdas' Kt/V values and Kt/V SDM. Barth's formula is simple, does not use an expression of a natural logarithm (as does the Daugirdas formula), and can be obtained with a simple pocket calculator in routine clinical practice. The Daugirdas logarithmic formula, on the other hand, because of its complexity, is not suitable for everyday clinical evaluation of HD adequacy. The calculation of the Daugirdas Kt/V value necessitates the use of a personal computer with specific software. Additionally, for the Kt/V Barth calculation there is no need for the ultrafiltration volume, duration of the dialysis treatment, or postdialysis body mass; only the pre- /postdialysis blood urea concentration is necessary. We could not demonstrate correlation between Kt/V Barth and ultrafiltration volume.

V. CONCLUSION

Since K/DOQI does recommend the Daugirdas second-generation formula for delivered dialysis dose (Kt/V) calculation, every dialysis center should obtain a personal computer with adequate software. Since the best correlations were seen between SDM Kt/V and the Daugirdas second generation Kt/V we can demonstrate that these two models are perfect than the other models. For routine clinical practice, however, we advise using the simple, nonlogarithmic Barth formula, which can be performed with a common pocket calculator. Last, every calculated Kt/V value should have bookmarks pertaining to both the calculation formula used and the postdialysis blood sampling method.

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